IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Civan *et al.*	:	Art Unit: 1614
Serial No.: 10/009,581	:	Examiner: Donna A. Jagoe
Filed: April 30, 2002	:	Confirmation No. 1751
For: Methods of Controlling Intraocular Pressure	:	

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

Sir:

This Appeal Brief is submitted with all necessary fees in support of the Notice of Appeal filed on April 10, 2008, and in Response to the Office Action dated January 11, 2008. An oral hearing is requested. No additional fee is believed to be due in this filing. However, if a fee is due, the Office is authorized to withdraw the necessary amount from Deposit Account 50-2424.

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FEE TRANSMITTAL for FY 2007

Patent fees are subject to annual revision.

☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT | **$770.00**

Complete if known	
Application Number	10/009,581
Filing Date	April 30, 2002
First Named Inventor	Civan et al.
Examiner Name	Donna A. Jagoe
Art Unit	1614
Attorney Docket No.	61169.00010 (L-2070)

METHOD OF PAYMENT *(check all that apply)*

☒ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☐ Deposit Account:
Deposit Account Number **50-2424**
Deposit Account Name **Montgomery, McCracken, Walker & Rhoads, LLP**

For the above-identified deposit account, the Director is hereby authorized to: *(check all that apply)*

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**
☒ Charge any additional fee required under 37 CFR 1.16 and 1.17 ☒ Credit any overpayments

FEE CALCULATION

1. Basic Filing, Search and Examination Fees

Application Type	Filing Fees	Small Entity	Search Fees	Small Entity	Examination Fees	Small Entity	Fees Paid
Utility	300	**155**	500	**255**	200	**105**	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. Excess Claim Fees

Fee Description	Fee	Small Entity
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee	Fee Paid	Multiple Dependent Claims Fee	Multiple Dependent Claims Fee Paid
* - 20 =	* x *	=			

Indep. Claims	Extra Claims	Fee	Fee Paid
* - 3 =	* x *	=	

3. Application Size Fee

If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof.

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee	Fee Paid
0 - 100 =	/ 50 =	* (round **up** to a whole number) x	250.00	**0**

4. Other Fee(s)

	Fees Paid
Non-English Specification, $130 fee (no small entity discount)	
Other: Appeal Brief and Request for Oral Hearing	$770.00

SUBMITTED BY

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Signature	Evelyn H. McConathy			Date	June 10, 2008

I. Real Party in Interest

Real Parties in interest are the Owners by Assignment: The Trustees of the University of Pennsylvania and The University of Otago, New Zealand.

II. Related Appeals and Interferences

Inventors, Mortimer Civan and Anthony McKnight, and Owners by Assignment, The Trustees of the University of Pennsylvania and The University of Otago in New Zealand, independently and collectively, along with their undersigned legal representative, are unaware of any appeals or interferences that are related to the instant Appeal or that will affect, be affected by, or have any bearing on, the Board's decision in the instant Appeal.

III. Status of the Claims

Claims 94 – 110, 112, 113, 115 and 116 are currently pending in the application. Claims 94 – 110, 112, 113, 115 and 116 stand rejected in the outstanding Office Action dated January 11, 2008.

As originally filed on 4/30/2002, the application was filed containing claims 1 – 37 as the national stage entry of PCT/US00/12551, which was filed on 5/8/2000 and claiming priority from Provisional Application No. 60/133,180, filed on 5/7/1999. Claims were amended by Preliminary amendment to conform to U.S. practice. Specifically, claims 2 – 37 were canceled and claims 38 – 93 were added, with claims 1, 56, 69 and 81 being the independent claims.

A first Office Action issued on August 1, 2003, with the Examiner rejecting claims 1 and 38 – 93. In a response on November 3, 2003, Applicants amended claims 1, 42, 43, 56, and 81, but no new claims were added.

On March 22, 2004 a Final Office Action issued rejecting claims 1 and 38 – 93. On July 22, 2004 Applicants canceled claims 56 – 67 and 69 – 91 while amending claims 1, 68, 92, and 93.

On August 11, 2005 The Examiner rejected claims 1, 38 – 55, 68, 92 and 93. An in-person Examiner Interview was conducted thereafter on October 27, 2005 with Applicant, Applicants' representative and Examiner participating. Applicants' invention was discussed as well as U.S. Patent No 5,215,991.

Following the in-person interview with the Examiner, Applicants submitted the Declaration of Dr. Mortimer Civan with an amendment on November 10, 2005. Claims 1 – 93 were cancelled by amendment, while claims 94 – 116 were added, with claims 94 and 108 being the independent claims.

On February 21, 2006 the Examiner issued an Office Action subjecting claims 94 – 116 to a restriction and/or election requirement. On March 21, 2006 Applicants elected, without traverse, to prosecute claims 94 – 107, drawn to a method of regulating intraocular pressure and further electing species. A Miscellaneous Action with SSP issued thereafter on June 14, 2006 seeking to further elect representative species encompassed by the claims. A correction to the election was filed by Applicants on July 14, 2006 to include additional agents elected for species.

On February 9, 2007 a second Miscellaneous Action with SSP issued seeking to further elect representative species encompassed by the claims following Applicants response to the restriction/election requirement. On March 7, 2007 a response to restriction requirement was filed by Applicants further electing species related to Group I encompassing claims 94 – 107.

On July 31, 2007 claims 94 – 113, 115 and 116 were rejected by the Examiner in a Final Office Action. Claim 114 was withdrawn. On October 31, 2007 Applicants responded with a request for continued examination. Claims 111 and 114 were cancelled by the response of October 31, 2008 accompanied by the RCE, and claims 94, 96, 103, 104, 107, 108, 112 were amended in the response.

On January 11, 2008 the Examiner issued an Office Action rejecting claims 94-110, 112, 113, 115 and 116 on the same grounds as the Final Action mailed July 31, 2007. On April 10, 2008 Applicants proceeded to file a Notice of Appeal for the rejection on the merits of pending claims 94 – 110, 112, 113, 115 and 116.

IV. Status of Amendments

No amendments have been made to the claims since Applicants' Response dated October 31, 2007.

V. Summary of the Claimed Subject Matter

Claims 94 – 110, 112, 113, 115 and 116 are pending in Applicants' application. Claims 94 and 108 are independent claims, and all other pending claims are directly or indirectly dependent upon either claim 94 or 108. As previously amended, the independent claims read as follows:

> 94. A method for regulating intraocular pressure by inhibiting sodium-hydrogen antiport activity in the eye of a human or animal subject in need of antiport regulation, the method comprising administering to ciliary epithelial cells of the eye of the subject having a trabecular network, a pharmaceutical composition comprising a pressure-modulating amount of at least one sodium-hydrogen exchange (NHE) inhibitor, and thereby inhibiting sodium-hydrogen antiport activity.
>
> 108. A method for regulating salt uptake or release by ciliary epithelial cells in an eye of a human or animal subject in need of regulating salt uptake or release in the cells, wherein said subject has a trabecular network, the method comprising controlling or modulating the function of one or more antiports of the ciliary epithelial cells of the aqueous humor by administering to the cells a modulating amount of a pharmaceutical composition consisting essentially of an NHE inhibitor, and thereby inhibiting salt uptake or release by the ciliary epithelial cells.

Support for Independent Claims 94 and 108

Element of Claim	Support for Element
Claim 94. A method for regulating intraocular pressure by inhibiting sodium-hydrogen antiport activity	See p. 6 lines 6 – 14.
in the eye of a human or animal subject	See p. 1, line 30 – p. 2, line 7.
the method comprising administering to ciliary epithelial cells of the eye of the subject	See p. 16, lines 28 – 32.
having a trabecular network	See p. 1, line 30 – p. 2, line 7.
a pharmaceutical composition comprising a pressure-modulating amount	See p. 16, line 28 – p. 17, line 5.
of at least one sodium-hydrogen exchange (NHE) inhibitor	See p. 13, lines 11 – 17.
thereby inhibiting sodium-hydrogen antiport activity	See p. 13, lines 11 – 17.
Claim 108. A method for regulating salt uptake or release by ciliary epithelial cells	See p. 11, lines 20 – 23.
in an eye of a human or animal subject	See p. 16, lines 28 – p. 17, line 5.
in need of regulating salt uptake or release in cells wherein subject has a trabecular network	See p. 2, lines 3 – 7.
the method comprising controlling or modulating the function of one or more antiports of the ciliary epithelial cells of the aqueous humor	See p. 6, lines 6 – 15; and p. 11 lines 20 – 26.
by administering to the cells a modulating amount of a pharmaceutical composition consisting essentially of an NHE inhibitor	See p. 5, line 31 – p. 6, line 5; and p. 13, lines 11 – 16.
thereby inhibiting salt uptake or release by the ciliary epithelial cells	See p. 6, lines 16 – 20.

As Applicants explain in the background of the invention, glaucoma results from the obstructed outflow from the aqueous humor of the eye, resulting in elevated intraocular pressure ("IOP") in the anterior chamber, and visual loss attributed to progressive damage of the optic nerve, producing a consequent loss of retinal ganglion cells. The aqueous humor of the eye is formed by the ciliary epithelium, comprising two juxtaposed cell layers: the outer pigmented ciliary epithelial (PE) cells facing the stroma, and the inner non-pigmented ciliary epithelial (NPE) cells contacting the aqueous humor. Thus, IOP reflects an imbalance between the rates of inflow (fluid formation) and outflow (fluid return) of the aqueous humor by re-absorption, and as

a result medical approaches to treating glaucoma are directed to reducing the net rate of formation of the aqueous humor.

The methods of the present invention recited at claims 94 and 108 are intended for the treatment of glaucoma and other conditions, which manifest elevated intraocular pressure in the eye of a patient, particularly human patients, but also include other mammalian hosts. The methods of the present invention recited at claims 94 and 108 are also intended for treatment of hypotonia and/or reduced intraocular pressure conditions of the eye, which may result form a variety of causes such as surgery for glaucoma, retinal detachment, uveitis and the like.

The present invention provides new understanding of the sodium/proton exchanger and its functional relationship with the chloride/bicarbonate exchanger (the "antiports"), regarding the uptake of salts from the body into the PE cells. More particularly, identifying and characterizing a sodium/proton exchanger as the antiport, permits strategies to be developed to use drugs at very low, focused concentrations for preventing, modulating or regulating intraocular pressure, most particularly for treating or reducing elevated intraocular pressure.

VI. Grounds for Rejection to be Reviewed on Appeal

1. Examiner's rejection of claim 101 under 35 U.S.C. §112, first paragraph, as failing to comply with the written restriction requirement. The Examiner asserts that claim 101 contains subject matter, in particular "precursor prostaglandins" that was not described in a way to reasonably convey to one skilled in the art that the inventor(s) had possession of the claimed invention.

2. Examiner's rejection of claims 94-96, 102 and 105-107 under 35 U.S.C. §102(b) as anticipated by U.S. Patent No. 4,950,591, issued to Cherksey.

3. Examiner's rejection of claims 94 and 102-105 under 35 U.S.C. §102(b) as anticipated by Drug Facts and Comparisons (1994).

4. Examiner's rejection of claims 94-96 and [99-113] 99 – 110, 112, 113 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,559,151, issued to Adorante et al and Cherksey.

5. Examiner's rejection of claims 94-98 and [102-113] 102 – 110, 112, 113 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,585,401, issued to Brandt et al and Cherksey

VII. Argument

Applicants respectfully submit that claims 94 – 110, 112, 113, 115 and 116 have been rejected in error. In the following sections, Applicants present arguments and evidence in support of their position. Some of the evidence is based on the Declaration of Dr. Mortimer Civan ("Civan") and attachments thereto, entered into the prosecution record under 37 C.F.R. § 1.132 on November 10, 2007, and duplicated in this Brief in the Evidence Appendix. All citations to this Declaration found in this Brief refer to the Evidence Appendix copy. Other evidence is presented from Applicants' record, which is also attached in this Brief in the Evidence Appendix.

1. Re: Claim Rejection under 35 U.S.C. § 112, first paragraph.

The Examiner has rejected claims 101 and 115-116 under 35 U.S.C. §112, first paragraph, under the written description requirement regarding Applicants' use of the term "precursor prostaglandins." In making this rejection, the Examiner appears to question whether Applicants have presented any prostaglandin precursor other than latanoprost. See Applicants' specification at page 3, lines 27-28.

It is well settled that while the purpose of §112, first paragraph, is to ensure that there is an adequate disclosure of the invention for which patent rights are sought and the purpose of the description requirement is to state what is needed to fulfill the enablement criteria, these requirements may be viewed separately but they are intertwined. *Kennecott Corp. v. Kyocera International, Inc.*, 5 USPQ2d 1194, 1197 (Fed. Cir. 1987) ("The written description must communicate that which is needed to enable the skilled artisan to make and use the claimed invention.")

Turning to the statement from Applicants' specification quoting the use of a prostaglandin precursor, refers to latanoprost at page 3, lines 15 – 28 as "another new type of drug . . . are also in current use." One of ordinary skill in the art would therefore, as part of his/her full knowledge, be familiar with such drugs if they are in current use, and would know which drugs are being referred to as a prostaglandin precursor for the stated purpose. Applicants have extended the definition of which drugs are intended by *exemplifying* latanoprost. Nowhere, however, do Applicants limit the claimed pharmaceutical composition to only latanoprost, nor are they so required by the law.

The courts have explained that "adequate description under the first paragraph of 35 U.S.C. §112 does not require literal support for the claimed invention. Rather, it is sufficient if the originally-filed disclosure would have conveyed to one of ordinary skill in the art that the appellant had possession of the concept of what is claimed." *Ex parte Parks*, 30 USPQ2d 1234, 1236 (BPAI 1993). Since the purpose of the law is to provide satisfaction of the description requirement to insure that subject matter presented in the form of a claim subsequent to the filing date of the application was sufficiently disclosed at the time of filing so that the prima facie date of invention can fairly be held to be the filing date of the application, Applicants have met this goal by not only providing the class of compositions referred to, but also an example of a member of the class known to the skilled practitioner.

> It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112. "A specification may, within the meaning 112, first paragraph, contain a written description of a broadlyof 35 U.S.C. claimed invention without describing all species that claim encompasses." *Utter v. Hiraga* 6 USPQ2d 1709, 1714 (Fed. Cir. 1988). "Representative samples are not required by the statute and are not an end in themselves." *In re Robbins*, 166 USPQ 552, 555 (CCPA 1970). *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

As further explained by the court in *In re Metcalfe*, 161 USPQ 789 (CCPA 1969), "under appropriate circumstances an applicant may describe a material used in a claimed invention by referencing materials sold under a particular trade name or trademark." In this case, Applicants have exemplified one of a class of prostaglandins precursor drugs "currently in use," by naming latanoprost. Thus, Applicants have met the written description requirement by identifying the prostaglandins precursor drugs as those which would be readily recognized by the intended practitioner.

2. <u>Re: Claim Rejections under 35 U.S.C. §102(b)</u>

The Examiner has rejected claims 94-96, 102 and 105-107 under 35 U.S.C. §102(b) as anticipated by Cherksey (US Patent No. 4,950,591). In making this rejection, the Examiner relies upon Cherksey for the teaching that amiloride is an agent that blocks ion transport and interacts with a sodium-hydrogen exchange inhibitor and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. See columns 1-3.

However, in response to the Examiner's conclusions, Applicants point out that Cherksey's patent is actually very narrow, dealing with a peptide isolated from normal membranes that he isolated and found to conform to amiloride-sensitive channels. Amiloride blocks the sodium channel well. In fact, Merck developed that drug for the purpose of blocking the sodium channel. As a result, Cherksey's claims are solely for the use of the isolated peptide as a diagnostic and experimental tool, whereas by comparison, Applicants' invention neither teaches, nor claims, a method for regulating the sodium channel or its role in aqueous humor formation.

It must be recognized that Cherksey discovered neither sodium channels, nor their sensitivity to amiloride. For example, Cherksey refers to the review of Palmer (who received his doctorate degree under Dr. Civan), on the subject of amiloride-sensitive sodium channels. In fact, amiloride was used as a blocker in the first demonstration that it blocked a sodium channel (Lindemann *et al.*, "Sodium-specific membrane channels of frog skin are pores: current fluctuations reveal high turnover," *Science* 21, 195(4275):292-4 (1977)). In the prior art, Dr. Civan reported that his ". . . results indicated that epithelial Na+ channels with a high affinity to amiloride likely contribute to reabsorption of solute from the aqueous humor" and that the "epithelial Na^+ channel is activated by shrinkage and contributes to unidirectional reabsorption as aqueous humor" (see, Abstract by Civan *et al.*, "Potential contribution of epithelial Na^+ channel to net secretion of aqueous humor," *J. Exp. Zool.*, 279:498-503 (1997)) (copy attached). This was the *first* evidence that amiloride-sensitive sodium channels were likely present in the nonpigmented (NPE) ciliary epithelial cells. See also the concluding sentence of Civan *et al.*, 1997, wherein it is explained that ". . . future approaches to the medical treatment of glaucoma could well focus on increasing the rate of unidirectional reabsorption in order to reduce net aqueous flow." In other words, the sodium channels (including amiloride-sensitive NPE sodium channels) underlie *reabsorption* of aqueous humor fluid, thus reducing the net rate of aqueous humor formation (net inflow).

Accordingly, the prior art teaches that blocking the sodium channel with amiloride *increases* inflow, *resulting in increased intraocular pressure* – which is contrary to the clinical intent of Applicants' invention. On the basis of that information, a knowledgeable practitioner would be led to *stimulate* the NPE sodium channels; not block them.

Applicants' claims are directed to inhibiting "sodium-hydrogen antiport activity" by administering to ciliary epithelial cells a pharmaceutical composition comprising or consisting essentially of a pressure-modulating amount of at least one "sodium-hydrogen exchange (NHE) inhibitor." Thus, Cherksey not only fails to anticipate Applicants' invention, it actually leads one away from what is taught by Applicants' patent application regarding regulation of the antiports. It also teaches away from what has been demonstrated in the prior art by Avila *et al.*, "Inhibitors of NHE-1 Na+/H+ exchange reduce mouse intraocular pressure," *Invest. Ophthalmol. Vis. Sci.* 43:1897-1902 (2002)) (demonstrating that the topical application of NHE inhibitors lowers IOP). Copy attached.

Moreover, Cherksey's speculation that amiloride-sensitive channels could be inhibited in dealing with many diseases, including glaucoma is unsupported and not enabled by the cited patent which teaches only methods relating to sodium channels. No evidence, let alone a rationale basis, is provided in the cited patent or anywhere in the prior art for such speculation, and others could not be taught by a mere speculation. More importantly, Cherksey neither mentions, nor suggests, that inhibiting or blocking NHE exchange would reduce aqueous humor inflow or intraocular pressure. Thus, the method taught by Cherksey fails to address each and every element of Applicants' claimed invention, and as such, the reference fails to anticipate the present invention.

3. <u>Re: Claim Rejections under 35 U.S.C. §102(b)</u>

The Examiner has also rejected claims 94 and 102-105 under 35 U.S.C. §102(b) as being unpatentable "Drug Facts and Comparisons" (1994). In making this rejection, the Examiner relies upon "Drug Facts and Comparisons" for teaching the use of timolol, which the Examiner defines as a beta blocker in reliance on the prior art and on Applicants' list at page 6, lines 23-26. However, as previously shown on the record, by cited prior art and by Declaration in Applicants' prior Response dated November 10, 2005, timolol was not, recognized by those knowledgeable in the field to be a sodium-hydrogen exchange (NHE) inhibitor.

Regardless of the Examiner's arguments that reduction of intraocular pressure is demonstrated by the use of timolol in "Drug Facts and Comparisons," the reference offers no evidence that timolol achieved any inhibition of sodium-hydrogen antiport activity *in the ciliary epithelial cells*. It describes a change in intraocular pressure, not any effect what-so-ever on the ciliary epithelial cells. In fact, the effect of any pharmaceutical composition on the antiports and

the effect of such treatment was unknown until its discovery by the present inventors, so it could not have been known or suggested by the art. As a result, nowhere in the prior art is there a suggestion that the antiports controlled fluid build up in the aqueous humor, and nowhere is there a suggestion that the NHE inhibitors could control the activity of the antiports. Yet, that is what is claimed by Applicants - not simply a possible effect on intraocular pressure.

Applicants have added to the previously claimed step of "administering" of the pharmaceutical composition in their claimed method, a second step that expressly requires" inhibiting sodium-hydrogen antiport activity" in the ciliary epithelial cells. This further emphasizes that, while "Drug Facts and Comparisons" may say that a small reduction of intraocular pressure was noted in the subject animal, the cited art does not offer any treatments of antiport activity – yet regulating antiport activity is expressly Applicant's invention – not simply reducing intraocular pressure. Thus, there is no need to read subject matter from the specification into the claims. It is now clearly stated.

This is not a case of inherency because while "Drug Facts and Comparisons" may report a reduction of intraocular pressure in the subject animal in conjunction with treatment, there is no way of knowing that that reduction was *a result of inhibition or regulation of antiport activity.* The Examiner asks on page 8 how Applicants can "bypass administering an eyedrop to the eye to administer said compositions to the ciliary epithelial cells of the aqueous humor." But then the Examiner turns to *Continental Can* to say that "a prior art reference may anticipate without disclosing a feature of the claimed invention, if that missing characteristic is necessarily present or inherent, in the single anticipating reference." How are these two concepts connected? Where is it described exactly how the change in intraocular pressure was tested by the authors of "Drug Facts and Comparisons" after what appears to be topical application?

In citing *Continental Can*, the Office must look at the entire holding of the decision, which further explains that

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA Inc. v. Monsanto,* 20 USPQ2d 1746, 1749 (Fed. Cir. 1991).

It cannot be assumed, without some evidence supporting the conclusion that the treatment by the authors of "Drug Facts and Comparisons" "could" have regulated or altered the antiport activity, or that such action on the antiports was inherent based upon the limited disclosure in the cited reference. If one were to use that definition, all things are inherent, because if you add enough links to what the inventors now disclose, there is nothing new under the sun. That of course, is not the basis for patent law; rather "new" discoveries are patentable.

It would appear that only Applicants' own invention has led to the conclusion that the treatment described in "Drug Facts and Comparisons" anticipates (inherently or otherwise) Applicants' claimed invention regarding the regulation of antiport activity within the eye. This is not a permissible basis for rejection. Applicants' claims are anticipated "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Brothers, Inc. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (BPAI 1987) (emphasis added).

4. Re: Claim Rejections under 35 U.S.C. §103(a) over Adorante and Cherksey.

The Examiner has rejected claims 94-96, and [99-113] 99 – 110, 112, 113 under 35 U.S.C. §103(a) as unpatentable over Adorante (US Patent No. 5,559,151) and Cherksey (US Patent No. 4,950,591). In making this rejection, the Examiner relies on Adorante for the use of 4,4'-diisothiocyanato-stilbene-2,2'-disulfonate (DIDS) to treat glaucoma and/or ocular hypertension, although the Examiner agrees that Adorante fails to suggest co-administration of NHE/NHE1 inhibitors. However, the Examiner further combines Cherksey with Adorante for the teaching that amiloride blocks ion transport and interacts with a sodium-hydrogen exchange inhibitor and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. The Examiner's conclusion is based on the premise that it would have been obvious to "employ two agents well known to treat glaucoma/ocular hypertension together to treat the very same condition."

In response, Adorante actually proposes the use of DIDS as a chloride-channel blocker of NPE cells, without any reference what- so-ever to bicarbonate-chloride exchange. This offers no relevance to blocking of sodium-proton exchange, and even the Examiner asserts that Adorante

fails to suggest administration of NHE/NHE1 inhibitors. Therefore, alone, Adorante has no effect on the patentability of Applicants' invention.

However, in this rejection, Adorante is not cited alone; it is combined with Cherksey. For the above stated reasons, Cherksey teaches a method for treating intraocular pressure by administering to affect the *sodium channels* of the eye, but that is not Applicants' invention, nor do Applicants' address the role of the sodium channel in aqueous humor formation. In fact, as explained above, if applied to Applicants' claimed invention, Cherksey would actually teach away from the invention. In addition, if the Office is tempted to find that the use of amiloride inherently teaches Applicants' invention, they are directed to *Jones v. Hardy* 220 USPQ 1020, 1025 (Fed. Cir. 1984) (The fact that a claimed invention is based on an inherent quality of a product well known in the art does not mean the invention is obvious as this confuses anticipation by inherency with obviousness).

Consequently, linking DIDS that blocks chloride channels (Adorante) with amiloride that blocks the ENaC sodium channel (Cherksey) would in no way lead one of skill in the art to try blocking sodium-proton exchange in order to reduce inflow at the antiports at the time of Applicants' invention. Even if combined, the combination fails to teach each and every element of Applicants' claimed invention. Since Cherksey fails to teach administering NHE/NHE1 inhibitors to the antiports, it cannot supplement the gap left by Adorante, and Adorante cannot render Applicants' invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 94-96, and 99-110, 112, 113 under 35 U.S.C. §103(a) be reconsidered and reversed.

5. <u>Re: Claim Rejections under 35 U.S.C. §103(a) over Brandt and Cherksey.</u>

The Examiner has rejected claims 94-98, and [102-113] 102 – 110, 112, 113 under 35 U.S.C. §103(a) as unpatentable over Brandt (US Patent No. 5,559,151) and Cherksey (US Patent No. 4,950,591). In making this rejection, the Examiner relies on Brandt for the use of an inhibitor of a Na^+-K^+-$2Cl^-$ (symport), such as butetanide, to treat glaucoma and/or ocular hypertension, although the Examiner agrees that Brandt fails to suggest co-administration of NHE/NHE1 inhibitors. However, the Examiner further combines Cherksey with Brandt for the teaching that amiloride blocks ion transport and interacts with a sodium-hydrogen exchange inhibitor and that amiloride and amiloride derivatives are capable of regulating membrane transport, cellular volume and other cellular pressure disorders. The Examiner's conclusion is

based on the premise that it would have been obvious to "employ two agents well known to treat glaucoma/ocular hypertension together to treat the very same condition.

In response, even if Brandt proposed the use of an inhibitor of a Na^+-K^+-$2Cl^-$ (symport), such as bumetanide, it is irrelevant to Applicants' invention. This is because Dr. Civan and others have demonstrated that bumetanide is, by itself, ineffective in lowering IOP. See, attached, Tian *et al.* "Effects of Adenosine Agonists on Intraocular Pressure and Aqueous Humor Dynamics in Cynomolgus Monkeys," *Exp. Eye Res.* 64:979-989 (1997) (demonstrating that bumetanide had no effect on IOP of live monkeys). Subsequently, Dr. Civan and associates demonstrated that bumetanide also has no effect on IOP of the live mouse, and it lowers IOP only if the sodium-proton exchange is also blocked (see, attached 2002 Avila *et al.*, reference in *Invest. Ophthalmol. Vis. Sci.* 43:1897-1902). Consequently, in light of the prior art at the time, Brandt's patent teaches that blocking the sodium-potassium-chloride co-transporter was the controlling factor in the process, not inhibition of sodium-proton exchange. Thus, Brandt has no relevance to blocking of sodium-proton exchange, and even the Examiner asserts that Brandt fails to suggest administration of NHE/NHE1 inhibitors. Therefore, alone, Brandt has no effect on the patentability of Applicants' invention.

However, in this rejection, Brandt is not cited alone. It is combined with Cherksey. But, for the above stated reasons, Cherksey teaches a method for treating intraocular pressure by administering to affect the amiloride-sensitive sodium channel, but that is not Applicants' invention, nor do Applicants' address the role of the sodium channel in aqueous humor formation. In fact, as explained above, if applied to Applicants' claimed invention, Cherksey would actually teach away from the invention.

Consequently, linking treatment of bumetanide as an inhibitor of a Na^+-K^+-$2Cl^-$ (symport) (Brandt) with amiloride that blocks the ENaC sodium channel (Cherksey) would in no way lead one of skill in the art to try blocking sodium-proton exchange in order to reduce inflow at the antiports at the time of Applicants' invention. Even if combined, the combination fails to teach each and every element of Applicants' claimed invention. In addition, if the Office is tempted to find that the use of amiloride inherently teaches Applicants' invention, they are directed to *Jones v. Hardy* 220 USPQ 1020, 1025 (Fed. Cir. 1984) (The fact that a claimed invention is based on an inherent quality of a product well known in the art does not mean the invention is obvious as this confuses anticipation by inherency with obviousness).

Since Cherksey fails to teach administering NHE/NHE1 inhibitors to the antiports, it cannot supplement the gap left by Brandt. Consequently, neither Brandt, nor the combination of Brandt and Cherksey, can render Applicants' invention obvious. Accordingly, Applicants respectfully request that the rejection of claims 94-96, and 102 – 110, 112, 113 under 35 U.S.C. §103(a) be reconsidered and reversed.

Applicants' Response to Examiner's Arguments

The presently cited prior art references as cited in the January 11, 2008 Office Action have been maintained over the previous Action, and as would be expected, many of the Examiner's arguments have also been maintained. As can be seen from the prosecution history, Applicants and the Examiner remain at odds over the meaning of each cited reference, the motivation to combine them in the manner proposed, and whether a combination of the references teaches each and every element of Applicants' invention.

Finally, the Examiner has discounted the points made in the Civan Declaration, attached hereto, by Dr. Civan, a recognized expert in the field of intraocular pressure and the treatments thereof, even though Dr. Civan's comments were supported by the published literature.

Accodingly, if neither the statement of law or scientific fact, including the Declaration of an expert in the field are found persuasive by the Examiner, then no argument made in this section in Response to the Examiner's comments will move this case forward, and intervention and interpretation by the Board of Appeals is required to move this claimed invention to allowance.

Conclusion

Thus, in light of the foregoing, the prior art fails to render Applicants' invention obvious, and Applicants respectfully request that, in light of the foregoing, the rejection of Applicants' method claims under 35 U.S.C. § 112, § 102(b) and § 103(a) be reconsidered and request that the Board reverse the rejections.

In sum, Applicants request, therefore, that all rejections be reconsidered and reversed by the Board for the reasons herein stated, and Applicants assert that all pending claims are in condition for allowance, and respectfully request that allowance be granted at the earliest date possible. No additional fee is believed to be due in this filing. However, if a fee is due, the Office is authorized to withdraw the necessary amount from Deposit Account 50-2424. Should the Board have any questions prior to oral hearing, it is encouraged to contact Applicants' undersigned representative at (215) 772-7550.

Respectfully submitted,

Civan *et al.*

Dated: June 10, 2008

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VIII. CLAIMS APPENDIX

As Amended in the Previous Response dated October 31, 2007

Claims 1-93 (Cancelled)

94. (Previously Presented) A method for regulating intraocular pressure by inhibiting sodium-hydrogen antiport activity in the eye of a human or animal subject in need of antiport regulation, the method comprising administering to ciliary epithelial cells of the eye of the subject having a trabecular network, a pharmaceutical composition comprising a pressure-modulating amount of at least one sodium-hydrogen exchange (NHE) inhibitor, and thereby inhibiting sodium-hydrogen antiport activity.

95. (Previously Presented) The method of claim 94, wherein the at least one sodium-hydrogen exchanger (NHE) inhibitor is a sodium-hydrogen exchanger isoform 1 (NHE1) inhibitor.

96. (Previously Presented) The method of claim 94, wherein the NHE inhibitor is selected from the group consisting of an amiloride, ethyl-isopropyl-amiloride (EIPA), dimethylamiloride (DMA), HOE694, methylpropylamiloride, and derivatives thereof.

97. (Previously Presented) The method of claim 94, wherein the pharmaceutical composition further comprises an inhibitor of a Na^+-K^+-$2Cl^-$ symport.

98. (Previously Presented) The method of claim 97, wherein the Na^+-K^+-$2Cl^-$ symport inhibitor is bumetanide.

99. (Previously Presented) The method of claim 94, wherein the pharmaceutical composition further comprises an anion exchanger isoform 2 (AE2).

100. (Previously Presented) The method of claim 99, wherein the inhibitor of anion exchanger isoform 2 is 4,4'-diisothiocyanatostilbene-2,2'-disulfonate (DIDS).

101. (Previously Presented) The method of claim 94, wherein the pharmaceutical composition further comprises at least one compound selected from the group consisting of miotics, beta blockers, carbonic anhydrase inhibitors, and precursor prostaglandins.

102. (Previously Presented) The method of claim 94, wherein administration of the pharmaceutical composition is topical, intravitreous, via an ocular insert, or via an implanted reservoir.

103. (Previously Presented) The method of claim 94, wherein the human or animal subject has glaucoma.

104. (Previously Presented) The method of claim 94, wherein the human or animal subject is subject to glaucoma.

105. (Previously Presented) The method of claim 94, wherein the pharmaceutical composition consists essentially of a pressure-modulating amount of at least one sodium-hydrogen exchange inhibitor.

106. (Previously Presented) The method of claim 105, wherein the at least one sodium-hydrogen exchanger (NHE) inhibitor is a sodium-hydrogen exchanger isoform 1 (NHE1) inhibitor.

107 (Previously Presented) The method of claim 105, wherein the NHE inhibitor is selected from the group consisting of an amiloride, ethyl-isopropyl-amiloride (EIPA), dimethylamiloride (DMA), HOE694, methylpropylamiloride, and derivatives thereof.

108. (Previously Presented) A method for regulating salt uptake or release by ciliary epithelial cells in an eye of a human or animal subject in need of regulating salt uptake or release in the cells, wherein said subject has a trabecular network, the method comprising controlling or modulating the function of one or more antiports of the ciliary epithelial cells of the aqueous humor by administering to the cells a modulating amount of a pharmaceutical composition consisting essentially of an NHE inhibitor, and thereby inhibiting salt uptake or release by the ciliary epithelial cells.

109. (Previously Presented) The method of claim 108, wherein the modulating effect is reversible upon cessation of administration of the NHE inhibitor.

110. (Previously Presented) The method of claim 108, wherein the pharmaceutical composition is administered to the cells *in vitro* or *in vivo*.

111. (Cancelled).

112. (Previously Presented) The method of claim 108, wherein the NHE inhibitor comprises amiloride or an amiloride derivative.

113. (Previously Presented) The method of claim 112, wherein the amiloride comprises either amiloride or ethyl-isopropyl-amiloride.

114. (Cancelled).

115. (Previously Presented) The method of claim 108, wherein an anion is transferred into the ciliary epithelial cells of the aqueous humor to block native chloride channels.

116. (Previously Presented) The method of claim 115, wherein the anion comprises cyclamate.

IX. EVIDENCE APPENDIX

TAB 1. Declaration of Dr. Mortimer M. Civan ("Civan Declaration") signed on August 29, 2006 and entered into the prosecution record under 37 C.F.R. §1.132 on August 30, 2006.

TAB 2. Chersky (US Patent No. 4,950,591), as cited by the Examiner.

TAB 3. "Drug Facts and Comparisons" (1994), as cited by the Examiner.

TAB 4. Adorante (US Patent No. 5,559,151), as cited by the Examiner.

TAB 5. Brandt (US Patent No. 5,585,401), as cited by the Examiner.

TAB 6. Civan, *et al.*, "Potential contribution of epithelial sodium channel to net secretion of aqueous humor," *J. Exp. Zool.*, 279:498-503 (1997), as cited by Applicants.

TAB 7. Avila, *et al.*, "Inhibitors of NHE-1 Na^+/H^+ exchange rates reduce mouse intraocular pressure," *Invest. Opthalmol. Vis. Sci.* 43:1897-1902 (2002), as cited by Applicants.

TAB 8. Tian, et al., "Effects of adenosine agonists on intraocular pressure and aqueous humor dynamics in cynomolgus monkeys," Exp. Eye Res. 64:979-989 (1997), as cited by Applicants.

X. RELATED PROCEEDINGS APPENDIX

The inventors, their respective Assignees (The Trustees of the University of Pennsylvania and The Univerisity of Otago in New Zealand), and Assignees' collective undersigned legal representative are unaware of any appeals or interferences that are related to the instant appeal, or that will affect, be affected by or have any bearing on the Board's decision in the instant appeal.

AUTHORIZATION

Applicants believe that no fees or extension of time are required for this submission. However, in the event that an extension of time is required, Applicants hereby submit a petition for such extension of time as may be necessary to make this response timely. The Commissioner is hereby authorized to charge any necessary fees to deposit account No. 50-2424. A duplicate of this Authorization is enclosed.

Respectfully submitted,
Civan *et al.*

Dated: June 10, 2008 By: Evelyn H. McConathy

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